Article

Efficacy of Conventional Transarterial Chemoembolization for Hepatocellular Carcinoma with Glass Membrane Emulsification Device

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Simple Summary: Transarterial chemoembolization (TACE) is the standard treatment for BCLC-B hepatocellular carcinoma (HCC). The porous glass membrane pumping emulsification device (GMD) produces a high percentage of water/oil emulsions with homogeneous and stable droplets, but there are few reports on the efficacy of GMD-conventional-TACE (GMD-c-TACE) for local recurrence. The present study indicates that the GMD-c-TACE for HCC could prevent early local recurrence and maintain hepatic functional reserve.

Abstract:

Background: Transarterial chemoembolization (TACE) is the standard treatment for BCLC-B hepatocellular carcinoma (HCC). A novel glass membrane emulsification device (GMD) produces a high percentage of water/oil emulsions with homogeneous and stable droplets. There are few reports on the efficacy of GMD-conventional-TACE (GMD-c-TACE); therefore, we aimed to evaluate the effectiveness of GMD-c-TACE.

Methods: Seventy-one patients with HCC with tumor diameter <5 cm who underwent c-TACE with and without GMD were included in this study to investigate local recurrence and hepatic functional reserve.

Results: The local recurrence rates of TACE without GMD were 3.0% at 6 months, 16.7% at 12 months, and 35.0% at 18 months, around where it plateaued. Hence, the local recurrence rates in the GMD-c-TACE group were 7.7% at 14 months and 23.1% at 20 months, respectively. Thus, GMD-c-TACE had a significantly lower local recurrence. Multivariate analysis showed that GMD-c-TACE could suppress local recurrence and maintain hepatic reserve.

Conclusions: GMD-c-TACE allows dense lipiodol accumulation in the tumor and attainment of good local control. Additionally, the inhibition of the release of anticancer drugs may maintain hepatic reserve. GMD-c-TACE is useful in preventing local recurrence and is expected to become the standard treatment form of c-TACE in the future.

Keywords: hepatocellular carcinoma; conventional transarterial chemoembolization; emulsion; lipiodol; glass membrane emulsification device

Introduction

Hepatocellular carcinoma (HCC) is the leading cause of cancer-related death, accounting for more than 700,000 deaths annually [1].

Transarterial chemoembolization (TACE) was developed in the early 1980s in Japan [2] and has become established as the standard treatment for hepatocellular carcinoma (HCC) that is not indicated for surgical resection or other forms of local therapy for patients with intermediate-stage HCC on the Barcelona Clinic Liver Cancer classification [**3-15].** The worldwide consensus on the technique for conventional transarterial chemoembolization is to mix ethiodized oil (Lipiodol; Guerbet, Villepinte, France) and doxorubicin/epirubicin solution by pumping using two syringes through a three-way stopcock [16, 17]. Ethiodized oil (Lipiodol; Guerbet, Villepinte, France) is widely used in TACE; it is not only a carrier of anticancer drugs but also has a role in embolization [18-22]. By mixing it with anticancer drugs into a water/oil emulsion, it can be possible to increase the gradual release of anticancer drugs and the embolization effect on target sites. The main local effects of TACE are local retention of anticancer drugs and Lipiodol and the resistive effect of the embolic substance. The better the accumulation of Lipiodol, the better the local control rate; thus, it is extremely important to improve Lipiodol accumulation in embolization therapy.

As Lipiodol is used as a drug carrier, drug properties should ideally be in a high-generation W/O (water in oil) state, but this may not be achievable in a previous three-way stopcock because the O/W (oil in water) and W/O areas are mixed.

In addition, the mixing ratio and pumping frequency of ethiodized oil and anticancer drug solution varied among operators and institutions, and the emulsion properties are not consistent. This means that the nature of the emulsion may be one of the background factors for differences in local control of HCC.

The porous glass membrane emulsification device (GMD) (MicroMagic; Piolax Medical Devices, Yokohama, Japan), which is a connector for adjusting W/O emulsion drug solutions, can produce stable and highly pure W/O emulsions that are used when mixing drug solutions and oil-based contrast media during TACE and injecting drugs evenly [23].

Improved accumulation of lipiodol is expected to maintain good local control of HCC and reduce the concentration of anticancer drugs leaking into the systemic circulation, thereby minimizing the impact of the treatment on liver function. TACE using GMD is expected to be clinically useful. However, there are no reports of efficacy compared between c-TACE with previous three-way stopcock and c-TACE with GMD [24].

This study investigated the outcomes and local recurrence factors in conventional-TACE (c-TACE) using GMD in c-TACE for HCC less than 5 cm in size.

Subjects and Methods

1. Subjects

The study included 71 patients with HCC (71 nodules) who had c-TACE at Saiseikai Niigata Hospital between January 2018 and November 2021. The diagnosis of HCC was made using dynamic contrast-enhanced computed tomography (CT) or dynamic contrast-enhanced magnetic resonance imaging (MRI).

The exclusion criteria were as follows: 1) tumor diameter greater than 5 cm, 2) intentionally incomplete TACE performed for massive or infiltrative tumors, 3) interval between TACE and the first follow-up CT more than 4 months, 4) no CT done during follow-up observation, 5) nodules with locoregional therapy such as percutaneous ethanol injection (PEI), microwave coagulation therapy, laser ablation, or radiofrequency (RF) ablation as an additional treatment before or after TACE, and 6) another treatment such as surgery, chemotherapy or radiotherapy before or after TACE.

We analyzed local recurrence and hepatic functional reserve in the 71 patients who underwent c-TACE due to intolerance to surgery, with or without GMD.

2. Methods

Treatment procedure

In all patients, the femoral artery was punctured by the Seldinger technique. After a 5 Fr introducer was inserted, a 5 Fr catheter was inserted, and a 3 Fr microcatheter (Attendant, Terumo, Tokyo, Japan) was advanced to the sub-area or further peripheral nutritional vessels by the coaxial technique. Conventional TACE with a three-way stopcock or a GMD was then performed.

TACE was performed according to the standard protocol for all patients. Epirubicin hydrochloride" 50 mg (Epirubicin; Nippon Kayaku, Tokyo, Japan) was dissolved in a nonionic contrast medium; the mixing ratio of aqueous Epirubicin solution to Lipiodol was 1:2. Emulsions were generated by pumping 20 times with a conventional three-way stopcock or GMD before intra-arterial administration. The emulsion was injected into the artery nourishing the tumor, and this was followed by subsequent embolization with 1-mm-diameter gelatin particles (Gelpart; Nippon Kayaku, Tokyo, Japan).

After embolization, multidirectional angiography confirmed the absence of tumor staining and the accumulation of Lipiodol in the tumor. The amount of the suspension used in both groups was determined according to the size of the nodule.

Immediately after the procedure, non-contrast CT examinations were performed using a 16-detector row scanner (Aquilion, Toshiba Medical Systems), and for lesion density measurement, a circular region of interest (ROI) lesion was set for each nodule, and the CT values of the Lipiodol that accumulated in the HCC nodule were measured. Patients were followed up after treatment to evaluate local recurrence and accumulation of Lipiodol, and CT was subsequently performed to determine whether there was a local recurrence.

Contrast-enhanced CT was performed 1 to 3 months after TACE and every 2 to 3 months after that to determine the response to treatment.

Local recurrence was defined as either 1) a non-lipiodol-accumulated area in the post-treatment tumor that was contrasted in the early contrast phase and showed low absorption in the delayed phase or 2) a low-absorption area in the delayed phase that was contrasted in the early contrast phase and was adjacent to the lipiodol-accumulated area.

Liver function including, albumin-bilirubin (ALBI)-score, was evaluated pre- and post-TACE procedure [25-28].

Ethical statements

This study was approved by the Institutional Review Board of Saiseikai Niigata Hospital and was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent before participating in the study.

Statistical analysis

The two groups were compared using the Chi-square test; normally distributed continuous data are presented as mean ± standard deviation, and then compared using a t-test. The differences in parameters were analyzed using a one-way repeated measures ANOVA. Recurrence rates were estimated using the Kaplan–Meier method and compared using the log-rank test. The Cox proportional hazard model analyzed the predisposing factors for recurrence.

Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Shimotsuke, Japan), a graphical user interfaces for R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria) [29].

Results

Patient Characteristics

Table 1 shows the clinical backgrounds of all patients. The mean age was 72.98 ± 9.67 years and the male-to-female ratio was 56:15, background liver factors HBV/HCV/AIH/Alc/NASH were 13/4/25/4/18/10, alpha-fetoprotein (AFP) was 21.96 ± 73.52 ng/mL, des-gamma-carboxy prothrombin (DCP) was 1083.06 ± 5212.065 mAU/mL, total bilirubin was 0.84 ± 0. 42 mg/dL, albumin was 3.84 ± 0.49 g/dL, prothrombin activity was 93.058 ± 12.98%, and ALBI-score was -2.52 ±.0.47. The median observation period was 255 days (71–1086 days).

Table 1. Clinical characteristics of patients enrolled in this study (*n* = 71).

Variables	Number or mean ±SD
Age (years)	72.986 ± 9.627
Gender (Male/Female)	56/15
Etiology (HBV/HCV/AIH/Alc/NASH)	14/25/4/18/10
Size (mm)	32.056 ± 5.997
Location (S1/2/3/4/5/6/7/8)	1/3/7/7/5/12/14/22
Total.bilirubin (mg/dL)	0.884 ± 0.423
Albumin (g/dL)	3.845 ± 0.498
DCP (mAU/mL)	1083.06 ± 5212.065
AFP (ng/mL)	21.966 ± 73.523
UICC stage (I/II/III)	4/49/18
ALBI score	-2.520 ± 0.470
Child-Pugh (5/6/7/8)	15/22/16/18
Post CT value (HU)	613.91 ± 312.65

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; AIH; autoimmune hepatitis; Alc, alcoholic hepatitis; NASH, non-alcoholic steatohepatitis; DCP, des-gamma-carboxy prothrombin; AFP, alpha-fetoprotein; UICC, Union Internationale Contre Le Cancer; ALBI score, albumin bilirubin score; HU, Hounsfield units

On assessing the background factors of the 27 patients in the three-way-stopcock-TACE group and the 44 patients in the GMD-c-TACE group, the mean age was 71.40 ± 8.94 and 73.95 ± 9. 97 years, respectively. The male-to-female ratios were 22:5 and 34:10, and the causes of liver disease HBV/HCV/AIH/Alc/NASH were 6/8/2/8/3 and 8/17/2/10/7, respectively. Other background factors include total bilirubin, albumin, prothrombin activity (%), alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelet count, AFP, DCP, and ALBI, which were not significantly different (Table 2). However, there was no significant difference between the two groups.

Table 2. Comparison between transarterial chemoembolization (TACE) therapy characteristics according to TACE devise.

Variables	Non -GMD (n=27)	GMD (n=44)	p-Value
Age (years)	71.407 ± 8.984	73.955 ± 9.977	p=0.2823
Gender (Male/Female)	22/5	34/10	p=0.673
Etiology(Viral/Non-viral)	14/13	25/19	p=0.683
Size (mm)	30.852 ± 6.532	32.795 ± 5.593	p=0.1869
Location (S1/2/3/4/5/6/7/8)	1/2/3/4/1/2/5/10	0/1/5/3/4/10/9/12	p=0.380
Total bilirubin (mg/dL)	1.002 ± 0.494	0.814 ± 0.362	p=0.0709
Albumin (g/dL)	3.733 ± 0.524	3.914 ± 0.475	p=0.1399
DCP (mAU/mL)	170.604± 436.403	1622.23 ± 6532.97	p=0.2632
AFP (ng/mL)	11.281 ± 13.285	28.280 ± 91.988	p=0.3537

UICC (I/II/III)	2/20/5	2/29/13	p=0.573
ALBI score	-2.384 ± 0.522	-2.601 ± 0.423	p=0.0616
Child-Pugh (5/6/7/8)	6/6/6/9	9/16/10/9	p=0.474
Lipiodol dose (ml)	3.344 ± 0.611	3.481 ± 0.587	p=0.349
Post CT value (HU)	527.67 ±303.91	670.16 ±329.31	p=0.074

Abbreviations: DCP, des-gamma-carboxy prothrombin; AFP, alpha-fetoprotein; ALBI score, albumin bilirubin score; UICC, Union Internationale Contre Le Cancer; HU, Hounsfield Unit.

Recurrence rate

Local recurrence was observed in 13 of the 71 nodes. The overall local recurrence rate was 3.0% at 6 months, 16.7% at 12 months, and 35.0% at 18 months, followed by a plateau (Figure 1, Log-rank test). The local recurrence rate in each group was 3.0% at 6 months, 16.7% at 12 months, and 35.0% at 18 months in the three-way stopcock-TACE (non-GMD) group, and 7.7% at 14 months and 23.1% at 20 months in the GMD-c-TACE group, and statistically significant differences were detected (Figure 2, Log-rank test).
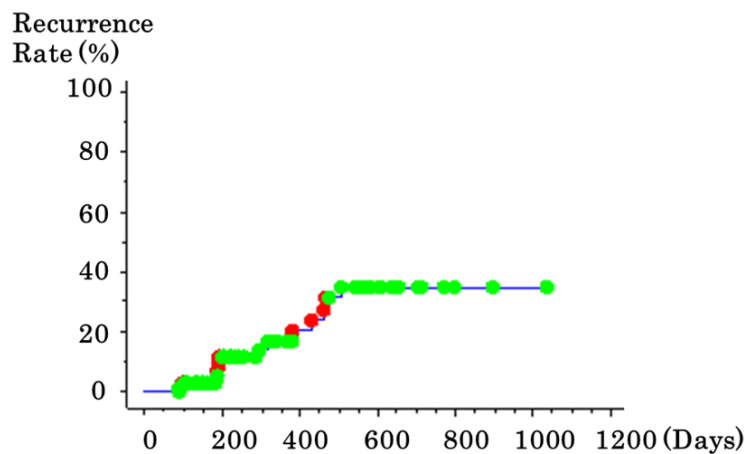

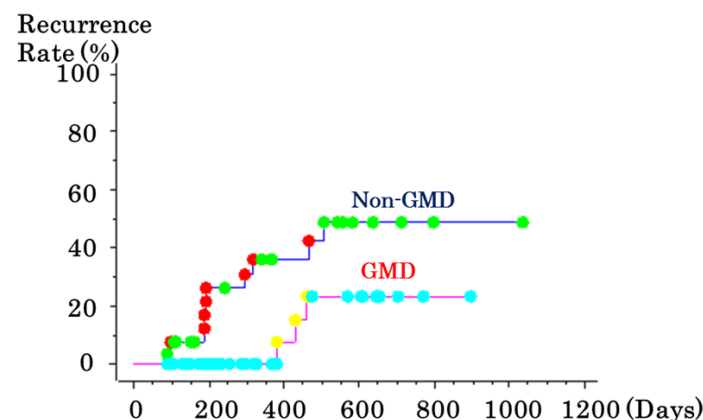**Figure 1.** Local recurrence after conventional TACE.

Figure 2. Local recurrence after conventional TACE according to TACE devise.

Although there were no significant differences in local recurrence rates by gender, age, background liver factors, tumor size, AFP, DCP, and post CT values, local recurrence was significantly higher in the non-GMD group, and multivariate analysis showed significant differences in recurrence by GMD use, which was related to the recurrence factor of c-TACE without GMD. The hazard ratio was 4.655 (Table 3).

Table 3. Prognostic factors related to local recurrence determined by multivariate analysis using Cox proportional hazard model.

Variable	Categories	HR	95% CI	p-Value
Gender	Male	1	0.135-4.431	P=0.7748
	Female	0.773		
Age	≧70 y.o	2.694	0.740-9.808	P=0.1328
	<70y.o	1		
Etiology	Viral	1	0.458-7.347	P=0.3914
	Non-viral	1.834		
Size(mm)	≧30mm	1	0.081-2.112	P=0.2886
	<30mm	0.414		
AFP (ng/mL)	≧10	1.689	0.343-8.325	P=0.5198
	<10	1		
DCP (mAU/mL)	≧100	1	0.099-3.760	P=0.5938
	<100	0.610		
Post CT (HU)	Low	1.337	0.299-5.977	P=0.7035
	High	1		
TACE devise	Non-GMD	4.655	1.192-18.171	P=0.0269
	GMD	1		

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; GMD, Glass Membrane Devise; AFP, alpha-fetoprotein; DCP, des-gamma-carboxy prothrombin; HU, Hounsfield Unit.

Changes in hepatic functional reserve

Although the overall hepatic reserve did not change after 3 months, the ALBI scores increased to 2.25±0.95 after 6 months and showed a significant difference (Figure 3, repeated one-way ANOVA).
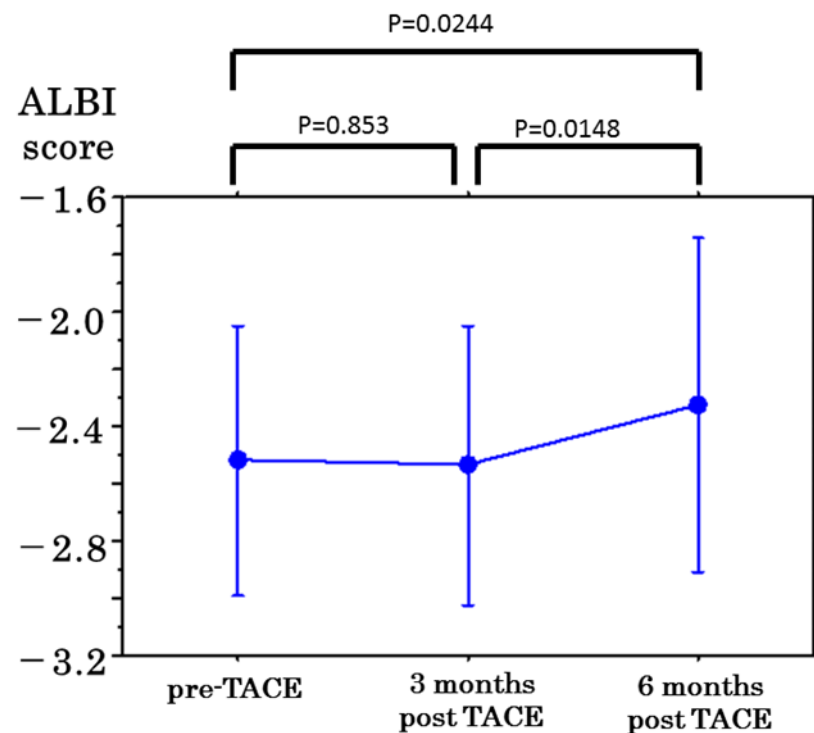
Figure 3. Dynamics of ALBI score in pre-TACE, 3months post TACE and 6 months post TACE.

Comparison of the groups showed that c-TACE with three-way stopcock resulted in deterioration after 6 months, whereas c-TACE with GMD significantly preserved hepatic reserve during the study (Figure 4, repeated one-way ANOVA).
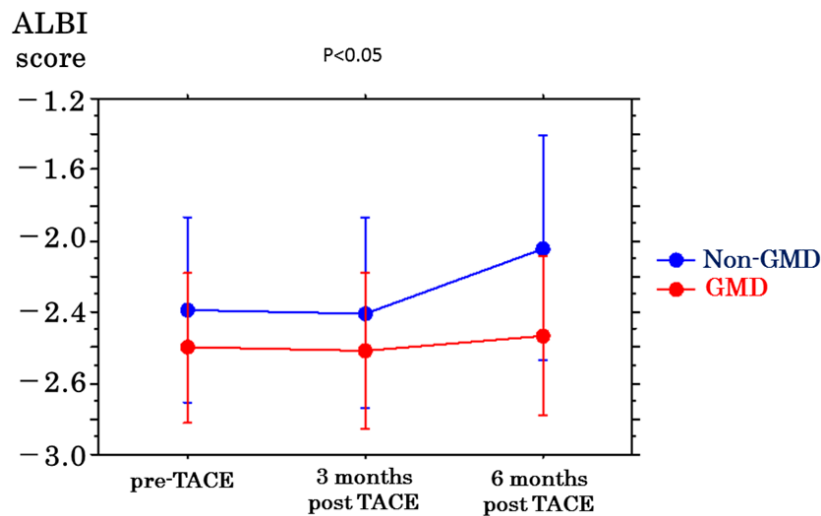
Figure 4. Dynamics of ALBI score in pre-TACE, 3months post TACE and 6 months post TACE according to TACE device.

Adverse events

Treatment-related adverse events were assessed according to the National Cancer Institute Common Terminology Criteria, version 4.0. Adverse events were evaluated as the maximum change in the grade within 3 months after therapy. In the three-way stopcock group (non-GMD), these events included an elevated AST level in 12 patients (44.4%), an elevated ALT level in 13 (48.18%), and hyperbilirubinemia in 1 patient (3.7%). In the GMD group, these events included an elevated AST level in 4 patients (9.1%), an elevated ALT level in 7 (15.9%), and thrombocytopenia in 1 patient (2.2%). All patients spontaneously healed without requiring additional treatment for elevated liver enzymes.

Discussion

According to the Barcelona Clinic Liver Cancer (BCLC) algorithm, TACE is the standard-of-care treatment in patients with intermediate-stage HCC [6, 12, 30, 31].

However, by definition, TACE is a palliative and iterative treatment, considering the low rates of complete response and the high risk of disease recurrence [10, 16, 17].

C-TACE using ethiodized oil (Lipiodol; Guerbet, Villepinte, France) has been performed worldwide for inoperable HCC since the 1980s [2, 18, 32, 33].

Forming Lipiodol–cytotoxic drug emulsions using a three-way stopcock is the standard technique of c-TACE. It involves pumping Lipiodol and doxorubicin/epirubicin solution emulsification using a three-way-stopcock. A published technical recommendation mentioned that the volume of doxorubicin/epirubicin solution should be lower than that of Lipiodol to create W/O emulsion [16]. It is widely known that the physicochemical characteristics of the emulsion can differ depending on the technical parameters. Previous studies focused on the type of emulsion ([W/O] or [O/W]) and demonstrated the advantages of W/O in c-TACE for HCC. W/O emulsion has been associated with a high embolic effect. It is known that the viscosity of W/O is higher than O/W [16, 19] ; a high viscosity can increase tumor retention [34]; and a high drug carriage capacity and longer drug release time [35, 36].

In c-TACE, it is known that the property of the emulsion is essential to controlling the drug release speed. W/O emulsion can release drugs slower when compared with O/W emulsion [37-39].

However, pumping emulsification using a three-way-stopcock has a critical limitation. The formed emulsion includes only approximately 70% W/O even when the mixture ratio of solution to Lipiodol is 1:2 [40]. Recently, a pumping emulsification device

with a microporous glass membrane was developed, which can create nearly a 100% W/O emulsion [23].

Theoretically, the pure W/O emulsion could achieve a slow drug release.

Furthermore, recent advances in systemic therapy for HCC have changed the indications for TACE, and c-TACE is now required to achieve more selective and better local control [41]. Therefore, how efficiently Lipiodol can be retained in tumor tissues is an important issue [38, 42, 43]. Lipiodol is an ethyl ester of iodized fatty acids of poppy-seed oil. It accumulates in HCC by improving permeability and retention in solid tumors. In combination with the embolization material, it blocks blood flow to the nutrient supply vessels of the HCC and the surrounding sinuses through intratumoral sinuses, resulting in ischemia and necrosis [44, 45]. The conventional pumping method using a three-way stopcock is widely used for the emulsification of water-soluble anticancer drugs and ethyl ester of iodinated poppy-seed oil fatty acid (Lipiodol), but this method can only achieve a W/O production rate of about 70% and the droplet size, and viscosity are unstable [40, 46].

From the perspective of TACE, this means that conventional TACE is more susceptible to the operator's technical factors than DEB-TACE, that the particle size is homogenized, and the drug load per particle is constant. Several issues are to be considered for the standardization of conventional TACE, including drug selection, emulsion properties, and treatment techniques. Homogenizing these as much as possible is essential in future discussions of TACE, and GMD was developed to enhance the effect of TACE by standardizing the emulsion preparing process that is performed in conventional TACE. That consists of a disk-shaped glass membrane made from volcanic ash with numerous 50 μm pores [23].

A porous glass membrane emulsification device (GMD) has been developed to enhance the therapeutic effect of conventional TACE. Porous glass membrane emulsification device (GMD) consists of a disk-shaped glass membrane made from volcanic ash with numerous 100 μm pores [48].

The use of GMD is expected to increase the therapeutic efficacy of TACE, as compared with the conventional three-way stopcock pumping, as it enables the production of a higher proportion of a W/O emulsion with more homogenous and stable droplets. It has been shown to be more effective in retaining anticancer drugs in tumors in the VX2 Rabbit liver cancer model [47].

As Lipiodol is used as a drug carrier, the drug properties are ideal for a state of W/O   with a high generation rate, but until now, the problem has been the mixture of O/W, as W/O areas are also present in a three-way stopcock system.

Based on these essential evaluations, GMD, which allows any operator to prepare stable emulsions, has the potential to offer the following advantages:

(1) Improved intravascular distribution with stable emulsion (even, smaller vessels, peripheral drug distribution)

(2) Improved intra-tumor stagnation rate due to viscosity.

(3) Sustained release effect of the drug; and

(4) Reduction of side effects (decrease in blood concentration of anticancer drugs [suppression of rapid increase] is expected.

Although better TACE outcomes are expected with GMD, its efficacy in clinical practice is still unclear.

In this study, local recurrence was observed in 13 of the total 71 nodes, and the overall local recurrence rate was 3.0% at 6 months, 16.7% at 12 months, and 35.0% at 18 months, after which it plateaued. The GMD-c-TACE group was 7.7% at 14 months and 23.1% at 20 months, showing that local recurrence could be suppressed significantly. In addition, when multivariate analysis was performed on the factors that suppressed local recurrence, GMD-c-TACE suppressed local recurrence and maintained hepatic reserve. Multivariate analysis also showed that non-GMD-c-TACE was the only factor related to local recurrence and showed a hazard ratio of 4.655.

Furthermore, the hepatic functional reserve was considerably preserved in the c-TACE group that used GMD. This is because the epirubicin penetration rate in the GMD W/O emulsion was significantly higher than that with the three-way stopcock, and the drug elution rate was substantially longer, resulting in fewer systemic effects [48].

The present study also showed that there were no Grade 4 or higher adverse events, no adverse events of clinical concern, and the hepatic reserve was maintained with GMD-c-TACE.

This study has several limitations. First, the number of patients was limited. Second, investigations of numerous patients in various stages of diseases are required. Thirdly, the retrospective design of this study may introduce bias in the selection of patients for HCC treatment. Finally, the data were from a single center, and selection bias cannot be ruled out. Confirmation of these findings will require a larger prospective clinical trial.

In conclusion, although further studies with a large number of patients at various disease stages are needed, GMD-c-TACE therapy can be considered to be a useful treatment strategy because of its ability to maintain the hepatic functional reserve. It also can homogenize the emulsion preparing process in c-TACE and move closer to standardization of the procedure.

Abbreviations: TACE: transarterial chemoembolization; GMD, glass membrane emulsification device; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; AIH; autoimmune hepatitis; Alc, alcoholic hepatitis; NASH, non-alcoholic steatohepatitis; DCP, des-gamma-carboxy prothrombin; AFP, alpha-fetoprotein; ALBI score, albumin bilirubin score

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